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ROBUST SUMMARY FOR DINITRILE CATEGORY**Summary****Identification of a structure based category**

The dinitrile category is composed of linear straight and branched chain alkanes with a common functional group, nitrile, at each end of the parent alkane chain. This category is composed of individual isomers containing six carbon atoms that differ by the position of the terminal nitrile groups. Dinitriles included in this group are ethylsuccinonitrile (ESN), 2-methylglutaronitrile (2-MGN), and adiponitrile (ADN). Structures of these dinitriles are presented below.

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<u>Chemical Name</u>	<u>CAS Registry Number</u>	<u>Structure</u>
Ethylsuccinonitrile Butanedinitrile, ethyl- (9CI)	17611-82-4	$\begin{array}{c} \text{CH}_2 - \text{CH}_3 \\ \\ \text{N} \equiv \text{C} - \text{CH}_2 - \text{CH} - \text{C} \equiv \text{N} \end{array}$
2-Methylglutaronitrile Pentanedinitrile, 2- methyl- (9CI)	4553-62-2	$\begin{array}{c} \text{CH}_3 \\ \\ \text{N} \equiv \text{C} - \text{CH}_2 - \text{CH}_2 - \text{CH} - \text{C} \equiv \text{N} \end{array}$
Adiponitrile Hexanedinitrile (9CI)	111-69-3	$\text{N} \equiv \text{C} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{C} \equiv \text{N}$

The terminal nitrile groups and limited chain length provide similar structure activity relationships with these materials. The ESN and 2-MGN isomers are by-products of ADN manufacture from 1,3-butadiene. ADN is being handled under the Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) Program but data will be presented in this document to lend overall support to the dinitrile category. Finally, in the data summaries, information will be presented that indicates these materials share similar physical chemical properties, environmental fate characteristics, ecotoxicity, and mammalian toxicity.

Scientific literature was searched and summarized (Table 1). Each study on category materials was evaluated for adequacy. Robust summaries were developed for each study addressing specific SIDS endpoints. Summaries were also developed for studies either considered not adequate but provided information of relevance for hazard identification and evaluation, or covered non-SIDS endpoints (Appendices A-C).

Table 1: Matrix of Available and Adequate Data on Dinitrile Category

	ADN	2-MGN	ESN
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	√	√	√
Boiling Point	√	√	√
Vapor Pressure	√	√	√
Partition Coefficient	√	√	√
Water Solubility	√	√	√
ENVIRONMENTAL FATE			
Photodegradation	√	√	√
Stability in Water	√	√	√
Transport (Fugacity)	√	√	√
Biodegradation	√	—/*	—/*
ECOTOXICITY			
Acute Toxicity to Fish	√	√	√
Acute Toxicity to Invertebrates	√	√	√
Acute Toxicity to Aquatic Plants	√	√	√
MAMMALIAN TOXICITY			
Acute Toxicity	√	√	√
Repeated Dose Toxicity	√	√	—/*
Developmental Toxicity	√	—/*	—/*
Reproductive Toxicity	√	—/*	—/*
Genetic Toxicity Gene Mutations	√	√	√
Genetic Toxicity Chromosomal Aberrations	√	√	—/*
√ = Data are available and considered adequate. — = No data available, or available data considered inadequate. —/* = No studies were available; however, we expect similar results to ADN.			

Evaluation of Data Matrix Patterns

The available adequate data were broken out by discipline (physical chemical, environmental fate, ecotoxicology, and mammalian toxicology). These comparisons were conducted to determine if a pattern existed among the materials and to determine if additional testing needed to be conducted to complete the data set for the category.

All three dinitriles have roughly equivalent physical chemical properties as a result of structural similarity. Complete and adequate data (Table 2) correlate well with structure and validate the category proposal.

Table 2: Physical and Chemical Characteristics

	<u>Adiponitrile</u>	<u>2-MGN</u>	<u>ESN</u>
Physical Appearance	Colorless liquid with a faint odor	Colorless, odorless liquid	Colorless to brown liquid
Molecular Weight	108.14	108.14	108.14
Water Solubility	80 g/L @ 20°C	40 g/L @ 20°C	22 g/L @ 23°C
Melting Point	1°C	-44 to -48°C	-39 to -43°C
Boiling Point	295°C	274°C	264°C
Vapor Pressure	6.8×10^{-4} mm Hg @ 25°C	5.1×10^{-3} mm Hg @ 25°C	0.019 mm Hg @ 25°C
Density/ Specific Gravity	0.9676 g/mL @ 20°C	0.95 g/mL @ 25°C	0.948 g/mL @ 25°C
Partition Coefficient (Log Kow)	-0.32	-0.644	0.28

Environmental fate data are essentially equivalent for the category members (Table 3). The data indicate that adiponitrile is inherently biodegradable. All 3 category members do not bioaccumulate. Fugacity model predictions indicate that these materials will act similarly in regards to partitioning in the environment. They will partition between soil and water with very little getting into air. Although tests on biodegradability have not been conducted for 2-MGN or ESN, it is reasonable to conclude that these materials would also be inherently biodegradable and thus no tests are recommended. The structural similarities between the compounds suggest that the nitrile moieties will have

similar biodegradation pathways and that the approach of extrapolating from ADN is valid. The completion of the repeated dose study on 2-MGN also strengthens the data for the overall category. The low molecular weight and relatively high vapor pressure for ESN suggest that it is likely not an issue for bioaccumulation. It appears that the predicted log Kow for ESN is in line with the properties and predicted Kows for the other 2 compounds. Given these observations, it is unnecessary to measure the log Kow of ESN.

Table 3: Environmental Fate

	<u>Adiponitrile</u>	<u>2-MGN</u>	<u>ESN</u>
Bioaccumulation*	Will not bioaccumulate BCF <1	Will not bioaccumulate BCF = 0.2	Low BCF = 3.162
Biodegradation	Inherently biodegradable	No Data	No Data
Fugacity*	Air: 0.037% Water: 30.2% Soil: 69.6% Sediment: 0.136%	Air: 0.875% Water: 45.9% Soil: 53.2% Sediment: 0.0765%	Air: 0.861% Water: 45.3% Soil: 53.8% Sediment: 0.767%
* = Modeled data			

Actual and estimated data on ecotoxicology support a category approach for these chemicals. A limited number of ecotoxicological studies have been conducted with dinitrile chemicals. Modeling of physical-chemical parameters (i.e., Kow) and aquatic toxicity was conducted to help provide insight into the behavior in the environment and the aquatic toxicity of adiponitrile, 2-MGN, and ESN (Table 4). Syracuse Research Corporation models for estimating physical-chemical properties were used to estimate log₁₀ Kow (Meylan and Howard, 1995) for the dinitrile chemicals for subsequent use in the ECOSAR program.

ECOSAR (Meylan and Howard, 1999) was used to estimate the missing aquatic toxicity data for the three dinitrile chemicals to green algae, daphnids (planktonic freshwater crustaceans), and fish, if necessary. ECOSAR predictions are based on actual toxicity test data for classes of compounds with similar modes of action, i.e., narcosis in the case of the dinitrile chemicals. Predicted log₁₀ Kow values were used as input for the ECOSAR model (see Table 4 for values). If actual measurements of Kow were available they are presented for comparative purposes. The available values were typically less than the estimated values and if these values were used for ECOSAR toxicity predictions would result in larger endpoint values (i.e., decreased toxicity) relative to the use of estimated Kow values.

Table 4: Aquatic Toxicity

	<u>Adiponitrile</u>	<u>2-MGN</u>	<u>ESN</u>
Log Kow	0.35 (E)* -0.32 (M)	-0.64 (E)	0.28 (E)
Toxicity to Fish (96-hour LC ₅₀ value)	2851 mg/L (E) 1930 mg/L (M)	3317 mg/L (E)	3317 mg/L (E)
Toxicity to Invertebrates (EC ₅₀ value)	2726 mg/L (48-hour, E) >1000 mg/L (48-hour, N)	3156 mg/L (48-hour, E) 1550 mg/L (24-hour, N)	3156 mg/L (48-hour, E) 831 mg/L (48-hour, N)
Toxicity to Algae (96-hour EC ₅₀ value)	1550 mg/L (E) >100 mg/L (72-hour NOEC, N)	1787 mg/L (E)	1787 mg/L (E)
*E = estimated value, N = value based on nominal test concentrations, M = measured test concentrations			

Results of the available aquatic test data with daphnids and fish for these compounds indicates that the daphnid 48-hour EC₅₀ was >800 mg/L and the 96-hour fish LC₅₀ was >1900 mg/L. Actual data suggest that algae may be the most sensitive of the three test species to the dinitrile chemicals, however, the 72-hour NOEC for adiponitrile was still >100 mg/L. The ECOSAR predictions of toxicity to the three species are in general agreement with the actual measured values when available. Based on the estimated and actual toxicity test data for the three chemicals, they do not represent an unacceptable risk to aquatic organisms.

Acute toxicity data indicates that all three chemicals exhibit similar acute toxicity (Table 5) and thus supports the category approach. In mammalian species, all 3 dinitriles are moderately toxic via the acute oral route. No specific target organs were identified for the 3 dinitrile compounds via the acute oral route; however, the study on ESN was the only acute oral study which included any necropsy evaluations. All deaths in the acute oral studies for the 3 dinitriles occurred between 1-3 days. Weight loss was observed in the adiponitrile study and clinical signs were observed in the adiponitrile and 2-MGN studies. Specific details are summarized in the robust summaries. Via the acute inhalation route, all 3 dinitriles exhibit similar toxicity (4-hour LC₅₀ or ALCs ranging from 0.66 mg/L to 1.4 mg/L) with 2-MGN exhibiting the higher toxicity of the 3 chemicals. Via the acute dermal route, both adiponitrile and 2-MGN are moderately toxic. Adiponitrile and 2-MGN are not dermal irritants and they both cause slight to

mild eye irritation. Adiponitrile was not a dermal sensitizer in guinea pigs. No data were available on 2-MGN for dermal sensitization. No data were available for ESN on dermal toxicity, dermal irritation, eye irritation, or dermal sensitization. The acute data that exists for these chemicals indicates that the chemicals produce similar toxicity profiles for acute toxicity.

Table 5: Acute Mammalian Toxicity

	<u>Adiponitrile</u>	<u>2-MGN</u>	<u>ESN</u>
Oral LD₅₀	138-301 mg/kg in rats	205 mg/kg in rats	Minimum lethal dose > 50 mg/kg and ≤ 500 mg/kg in rats
Inhalation LC₅₀	4-hour LC ₅₀ = 1.71 mg/L in rats	4-hour LC ₅₀ = 0.66 mg/L in rats	4-hour ALC = 1.4 mg/L in rats
Dermal LD₅₀ or LD₀	24-hour LD ₅₀ = 2134 mg/kg in rabbits	24-hour LD ₅₀ = 776 mg/kg in rabbits	No Data
Dermal Irritation	Not an irritant	Not an irritant	No Data
Eye Irritation	Slight irritant	Mild irritant	No Data
Dermal Sensitization	Not a sensitizer	No Data	No Data

Summary of the available data on repeated dose, developmental, and reproductive toxicity is shown in Table 6. Repeated exposure studies in rats have identified advanced adrenal degeneration in rats exposed to 0.5 ppm ADN in the drinking water for 2 years. A 13-week inhalation study in rats did not produce any compound-related microscopic lesions at concentration levels up to 99 mg/m³. Females at 99 mg/m³ had mildly decreased red blood cells, hemoglobin, and hematocrit levels. The NOEL for the 13-week inhalation study in rats was 30.6 mg/m³. Adiponitrile is not a developmental or reproductive toxin in the rat. A 4-week inhalation study of 2-MGN in rats revealed weight gain depression at 200 mg/m³. Minimal decreases in red blood cells, hemoglobin, and hematocrit values at 200 mg/m³ were accompanied by statistically significant increases in reticulocytes. The increases in reticulocytes were not considered adverse. No clinical or pathologic effects and no effects on neurobehavioral tests were observed in the study at any dose level tested. The NOAEL for the 2-MGN repeated dose study was 25 mg/m³. No data are currently available on repeated dose toxicity for ESN, or developmental and reproductive toxicity of 2-MGN or ESN. Because of the similarities observed between the 3 materials in their structures, physical and chemical characteristics, acute toxicity, environmental fate, and aquatic toxicity, and the similar NOAELs observed in the repeated dose studies of ADN and 2-MGN, it is reasonable to

conclude that ESN would have similar toxicity in repeated dose toxicity, and 2-MGN and ESN would have similar toxicity in developmental toxicity, and reproductive toxicity.

Table 6: Repeated Dose, Developmental, and Reproductive Toxicity

	<u>Adiponitrile</u>	<u>2-MGN</u>	<u>ESN</u>
Repeated Dose Toxicity (NOAEL)	30.6 mg/m ³ in a 13-week inhalation study in rats	25 mg/m ³ in a 4-week inhalation study in rats	No Data
Developmental Toxicity	Not a teratogen	No Data	No Data
Reproductive Toxicity	Not a reproductive toxin	No Data	No Data

Genetic toxicity data are similar between the 3 dinitriles, supporting a category approach (Table 7). Adiponitrile was not active genetically in a series of tests developed to detect either point mutations or clastogenicity. 2-MGN was weakly mutagenic in an *in vitro* bacterial reverse mutation assay and negative in an *in vivo* mouse micronucleus test. ESN was not mutagenic in an *in vitro* bacterial reverse mutation assay. While no data were available on the clastogenicity of ESN, it can be reasonable concluded that ESN would be inactive.

Table 7: Genetic Toxicity

	<u>Adiponitrile</u>	<u>2-MGN</u>	<u>ESN</u>
Mutagenic	No	Weakly	No
Clastogenic	No	No	No Data

Overall, the toxicologic database for adiponitrile is complete and the information available does not seem to suggest a high level of biological activity. The toxicologic database for 2-MGN and ESN are somewhat limited, but the information available suggests a level of toxicity comparable to adiponitrile. The 3 chemicals are similar in chemical structure, physical and chemical characteristics, environmental toxicity, aquatic toxicity, and acute toxicity. Because of these similarities, it is reasonable to conclude that the category members would behave similarly in the areas where data gaps are evident: biodegradation (2-MGN and ESN), repeated dose (ESN), developmental toxicity (2-MGN and ESN), reproductive toxicity (2-MGN and ESN), and clastogenicity (ESN).

TEST PLAN: No additional toxicity testing will be conducted.

Exposure Assessment for Dinitriles (2-MGN & ESN)

2-Methylglutaronitrile (2-MGN) is a chemical intermediate synthesized in the production of Adiponitrile. 2-MGN is manufactured at two facilities, the Victoria Site & Sabine River Works (SRW). The Crude 2-MGN from SRW is shipped to the Victoria Site. The Victoria Site refines approximately 92.5% of the MGN and a toller refines 7.5% to make Refined MGN. 99.9949% of the Refined MGN is shipped to DuPont's Maitland Site in Canada and is consumed in the production of 2-methylpentamethylenediamine. 0.005% is sent to a toll manufacturer where it is completely consumed in the production of a new chemical. 0.0001% of the Refined MGN was sold to an outside customer for testing. 2-Ethylsuccinonitrile (ESN) is an impurity in 2-MGN and is found in levels between 0 to 2% in the Refined MGN.

DuPont sites that produce and use MGN have effective safety, health & environmental practices and procedures in addition to engineering controls, environmental controls, and personal protective equipment to control exposure. Both manufacturing facilities have from 250 to 2000 personnel (construction, contractor, and plant employees) working on site. The areas where the substances are manufactured have from two to five operators during normal operations and up to a total of 60 people during a shutdown or major construction activity. Adequate safety equipment, such as safety showers, eyewash fountains, and washing facilities, are available in the event of an occupational exposure. Individuals handling 2-MGN should avoid contact with eyes, skin, and clothing, thoroughly wash any exposed area of the skin after handling, and avoid breathing any dust. Workers use butyl gloves and Tychem 9400 acid suits. They are not required to wear respirators during the routine operation of the plant. The potential for exposure of 2-MGN is the greatest during the loading and unloading of the MGN since the processes used are closed. The toll manufacturer and customer also have procedures, practices, and controls in place to manage the risk of exposure and no incidents have been reported to DuPont. DuPont practices Responsible Care[®] and assesses the ability of a potential toll manufacturer and customers to safely handle MGN prior to commencing a commercial relationship. This assessment includes reviews and audits of PPE (personal protective equipment), safety equipment and procedures, structural integrity, and safety practices.

Air monitoring has been conducted on 2-MGN but samples are not analyzed for ESN, since rarely even a trace is detected in air samples. Time-weighted averages (TWA) samples are trapped using tertbutylcatechol treated charcoal tubes, desorbed with 5% acetone in carbon disulfide, and analyzed using gas chromatography. The accuracy of the overall analysis is reported to be 10% when the sampling pump is calibrated with a charcoal tube in line. LOGAN (lognormal analysis) is a computerized statistical method for characterizing occupational exposures to chemicals, noise, and other environmental hazards. LOGAN uses sequential collection of data and makes decisions on the minimum amount of data. It helps make cost-effective, accurate decisions that ensure a healthy workplace. LOGAN uses inferential statistics to estimate the true workplace conditions, in the same way that public polling estimates opinions by sampling a

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representative percentage of the public. LOGAN is designed to limit the risk of employee occupational overexposure to less than 5%.

No DuPont Acceptable Exposure Limit has been established for Ethylsuccinonitrile. The DuPont Acceptable Exposure Limit for 2-MGN is 1 ppm as an 8-hour TWA. No other limits have been established. None of the samples taken suggest the probability of exposure in excess of the current recommended AEL of 1 ppm 8-hour TWA.

EXPOSURE DATA

ADN PLANT

2-Methylglutaronitrile is manufactured in the ADN plant.

ADN Production Operators				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
88	134	0.0100	0.0096	0.0100

ADN I&E Maintenance				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
28	18	0.0099	0.0081	0.0100

ADN Maintenance Mechanics				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
39	91	0.0104	0.0081	0.0400

HMD PLANT

The HMD plant occasionally refines 2-methylglutaronitrile as a batch operation. The HMD filtration operator is responsible for the injection wells and waste area.

HMD Production Operators				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
32	121	0.0099	0.0090	0.0100

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HMD I&E Maintenance				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
12	10	0.0096	0.0082	0.0100

HMD Maintenance Mechanics				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
20	22	0.0098	0.0094	0.0100

POWER HOUSE EAST

The powerhouse production operators burn some dinitrile waste streams in the boilers.

Power House Production Operators				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
17	11	0.0100	0.0097	0.0100

OLA PACKAGING WAREHOUSE

Contractor operators at the packaging warehouse and the landfills packages waste solids and ships the solids to landfill

Zachry/Sentinel Packaging Warehouse				
<u>People</u>	<u>No. of Results</u>	<u>Avg. of TWA (ppm)</u>	<u>Min. of Results (ppm)</u>	<u>Max. of Results (ppm)</u>
2	12	0.0093	0.0088	0.0100

References for the Summary:

Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92.

Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).